

**CLAIMS**

1. Device (10) for measuring the electrical activity of at least one biological element, comprising  
5 a substantially plane substrate (12), which has a lower face (1) and an upper face (3) and which has at least one through opening (120) for housing this biological element (18), said opening being delimited by a set of walls (16, 26, 36), characterized in that:

10 - it comprises two substantially plane plates (11, 13) that are placed on either side of the lower and upper faces of the substrate and that delimit with said set of walls a chamber (19) which is filled, when the device is being used, with a liquid medium ;

15 - each of the plates is provided, on its face lying opposite the substrate, with at least one electrode (110, 130) facing the opening in the substrate ;

20 - each of the plates further has at least one channel (111, 131, 132) that starts inside said chamber and connects the latter to the outside of the device ; and

25 - the chamber communicates with the outside of the device only through said channels.

2. Device (10) according to claim 1, characterized in that the opening (120) in the substrate (12) comprises an upper part (35), a central part (25) and a lower part (15) that are coaxial, the upper and central parts forming a cup (40) for housing the biological element (18), whereas the lower part

forms a reservoir (60) for housing a volume of liquid medium sufficient to create therein, by suction, a vacuum suitable for forming a high-resistance seal between said element and said cup.

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3. Device (10) according to claim 2, characterized in that the upper part (35) of the opening (120) in the substrate (12) is of frustoconical shape, whereas the central part (25) of this opening is 10 of cylindrical shape.

4. Device (10) according to claim 3, characterized in that the upper part (35) of the opening (120) in the substrate (12) has its largest 15 diameter between 20 and 100 microns and its smallest diameter between 10 and 30 microns and has a height of between 10 and 50 microns, whereas the central part (25) of this opening has a diameter of between 0.1 and 3 microns and a height of 100 microns or less.

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5. Device (10) according to claim 3, characterized in that the upper part (35) of the opening (120) in the substrate (12) has its largest diameter between 500 microns and 1.5 mm and its 25 smallest diameter between 200 and 600 microns and has a height of between 300 microns and 10 mm, whereas the central part (25) of this opening has a diameter of between 0.1 and 3 microns and a height of 100 microns or less.

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6. Device (10) according to any one of

claims 2 to 5, characterized in that the lower part (15) of the opening (120) in the substrate (12) is cylindrical and measures between 10 and 100 microns in diameter for a height of 300 to 700 microns.

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7. Device (10) according to any one of the preceding claims, characterized in that the substrate (12) is made of one or more micromachinable materials.

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8. Device (10) according to claim 7, characterized in that the substrate (12) is based on silicon.

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9. Device (10) according to any one of the preceding claims, characterized in that the substrate (12) is formed from two silicon wafers (121, 123) that are placed on either side of an intermediate membrane (122) which they are fastened to.

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10. Device (10) according to claim 9, characterized in that the intermediate membrane (122) is made of an insulating material or of a silicon wafer coated on its various faces by an insulating material.

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11. Device (10) according to claim 10, characterized in that the insulating material is silicon dioxide or silicon nitride.

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12. Device (10) according to any one of claims 9 to 11, characterized in that the upper part (35) of the opening (120) in the substrate (12) is

delimited by the wall (36) of a through recess made in one of the silicon wafers (121, 123) that are placed on either side of the intermediate membrane (122), whereas the lower part (15) of the opening (120) of the 5 substrate (12) is delimited by the wall (16) of a through recess made in the other of said silicon wafers.

13. Device (10) according to any one of  
10 claims 9 to 12, characterized in that the central part (25) of the opening (120) in the substrate (12) is delimited by the wall (26) of a trough recess made in the intermediate membrane (122).

15 14. Device (10) according to any one of claims 9 to 12, characterized in that the central part (25) of the opening (120) in the substrate (12) is delimited at the same time by a first cylindrical wall (26) corresponding to the wall of a through recess made 20 in the intermediate membrane (122) and by a second cylindrical wall (50) protruding from the first cylindrical wall towards the upper face (3) of the substrate.

25 15. Device (10) according to any one of claims 2 to 10, characterized in that the upper face (3) of the substrate (12) is covered with a film (126) that is made of a biocompatible material and is provided with at least one through opening (127), this 30 opening being coaxial with the upper part (35) of the opening (120) in the substrate, with the same geometry

as it but with a larger cross section.

16. Device (10) according to claim 15,  
characterized in that the opening (127) in the film  
5 (126) is frustoconical and has its largest diameter  
between 500 microns and 1.5 mm and its smallest  
diameter between 200 and 600 microns and has a height  
of between 300 microns and 1 mm.

10 17. Device (10) according to any one of the  
preceding claims, characterized in that the plates (11,  
13) lying on either side of the lower and upper faces  
of the substrate are made of an insulating material and  
in that the electrodes (110, 130) carried by these  
15 plates are plane electrodes, especially Ag/AgCl<sup>-</sup>  
contacts.

18. Device (10) according to any one of the  
preceding claims, characterized in that the plate (13)  
20 lying opposite the upper face (3) of the substrate (12)  
has two channels (131, 132).

19. Device (10) according to any one of the  
preceding claims, characterized in that the plate (11)  
25 lying opposite the lower face (1) of the substrate (12)  
has only one channel (111). .

20. Device (10) according to claim 18,  
characterized in that the channels (131, 132) of the  
30 plate (13) lying opposite the upper face (3) of the  
substrate (12) pass through the thickness of said

plate.

21. Device (10) according to any one of the preceding claims, characterized in that the channel 5 (111) of the plate (11) lying opposite the lower face (1) of the substrate (12) passes through the thickness of said plate.

22. Device (10) according to claim 18,  
10 characterized in that the channels (131, 132) of the plate (13) lying opposite the upper face (3) of the substrate (12) circulate within the thickness of this plate, substantially parallel to the faces of said plate, until reaching one of the edges of said plate.

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23. Device (10) according to claim 18,  
characterized in that the channel (111) of the plate  
10 (11) lying opposite the lower face (1) of the substrate  
(12) circulate within the thickness of this plate,  
20 substantially parallel to the faces of said plate,  
until reaching one of the edges of said plate.

24. Device (10) according to any one of the preceding claims, characterized in that the opening 25 (120) in the substrate (12), the electrodes (110, 130) carried by the plates (11, 13) lying on either side of the lower and upper faces of this substrate and the channel (111) of the plate (11) lying opposite the lower face (1) of the substrate are coaxial.

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25. Device (10) according to any one of the

preceding claims, characterized in that it comprises means (4, 5) for sealing the chamber (19) and for damping the electrical noise and the vibrations emanating from the surrounding medium.

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26. Device (10) according to claim 25, characterized in that the means for sealing the chamber and for damping the electrical noise and the vibrations emanating from the surrounding medium consist of a  
10 first gasket (4), that is inserted between the substrate (12) and the plate (11) lying opposite the lower face (1) of this substrate, and of a second gasket (5), that is inserted between the substrate (12) and the plate (13) lying opposite the upper face (3) of  
15 this substrate, each of these gaskets being provided with at least one perforation (140, 150) which is arranged and dimensioned so as to circumscribe the electrode on the plate with which it is in contact.

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27. Device (10) according to claim 25 or claim 26, characterized in that the substrate (12), the plates (11, 13) lying on either side of the lower and upper faces of this substrate (12), and the means (4, 5) for sealing the chamber and damping the electrical  
25 noise and the vibrations emanating from the surrounding medium are modules that are assembled in a removable manner.

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28. Device (10) according to claim 27, characterized in that it includes means (6, 7) for holding the substrate (12), the plates (11, 13) that

lie on either side of the lower and upper faces of this substrate and the means (4, 5) for sealing the chamber and damping the electrical noise and the vibrations emanating from the surrounding medium, in place in the 5 assembled condition.

29. Device (10) according to any one of the preceding claims, characterized in that, when this device is intended for measuring the electrical 10 activity of several biological elements in parallel :

- the substrate (12) has a number of identical through openings (120) uniformly spaced apart ;

- the plates (11, 13) lying on either side 15 of the lower and upper faces of this substrate are printed circuits that are each provided with as many electrodes (110, 130) as the substrate (12) has through openings ;

- the plate (11) lying opposite the lower 20 face of the substrate has at least as many channels (111) as the substrate (12) has through openings ; and

- the plate (13) lying opposite the upper face of the substrate has at least as many channels (131) for introducing substances and at least as many 25 channels (132) for removing substances as the substrate has through openings.

30. Device (10) according to claim 29, characterized in that it includes two identical gaskets 30 (4, 5), each provided with as many perforations as the substrate (12) has through openings (120).

31. Device (10) according to claim 30,  
characterized in that it includes two identical clamps  
(6, 7) that fit over the edges of the stack formed by  
5 the substrate (12), the plates (11, 13) lying on either  
side of the lower and upper faces of this substrate and  
the gaskets (4, 5).

32. Application of a device (10) as defined  
10 in any one of claims 1 to 31 for screening molecules  
for therapeutic purposes.

33. Application of a device (10) as defined  
in any one of claims 1 to 31 for diagnosing pathologies  
15 associated with an ion channel dysfunction.

34. Application of a device (10) as defined  
in any one of claims 1 to 31 for detecting toxic  
substances.

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35. Application of a device (10) as defined  
in any one of claims 1 to 31 for detecting living cells  
or cells having their membrane integrity preserved.

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36. Application of a device (10) as defined  
in any one of claims 1 to 31 for detecting dead cells  
or cells having lost their membrane integrity.

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37. Application of a device (10) as defined  
in any one of claims 1 to 31 for detecting the release  
of substances from cells by exocytosis.

38. Application of a device (10) as defined in any one of claims 1 to 31 for measuring a variation of membrane capacitance resulting from the fusion of a  
5 cell with another cell or with a vesicle.

39. Application of a device (10) as defined in any one of claims 1 to 31 for stimulating cells.

10 40. Application of a device (10) as defined in any one of claims 1 to 31 for studying the intracellular activity of a cellular network, or of a tissue or of a cellular co-culture.

15 41. Application of a device (10) as defined in any one of claims 1 to 31 for studying the response of cells A to an electrical stimulation applied to cells B.

20 42. Application of a device (10) as defined in any one of claims 1 to 31 for studying mechanical-sensitive ion channels with the view to providing "mechanical" sensors.